Tumor Size as a Prognostic Indicator of Histologic Grade of Soft Tissue Sarcoma

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Background and Objectives: Tumor size is one of the independent factors affecting prognosis of patients with soft tissue sarcoma (STS). We evaluated the significance of tumor size in combination with tumor depth in each histologic grade.

Methods: A total of 162 adult patients with localized STS in the extremities and trunk were selected. Patient ages ranged from 15 to 84 (median 46.5) years with a male-to-female ratio of 1.19. Histologic grade of tumors was low in 53 cases, intermediate in 51, and high in 58. Two types of categorization were set, and their significance in predicting the prognosis of patients in each grade was evaluated. In the first category (intermediate grade), tumors were dichotomized at 10 cm: Group A comprised patients with deeply seated tumors measuring >10 cm; Group B comprised patients other than those in Group A. In the second category (high grade), tumors were dichotomized at 5 cm: Group C comprised patients with deeply seated tumors measuring >5 cm; Group D comprised patients other than those in Group C.

Results: Categorization was not useful in the prognosis of low grade tumors. In the intermediate grade group, the 5-year survival rate of Group B patients (78%) was higher than in Group A patients (59%) ($P < 0.05$), showing that dichotomization at 10 cm was useful. In the high grade group, the 5-year survival rate in Group C patients (32%) was lower than in Group D patients (56%), showing that dichotomization at 5 cm was useful.

Conclusions: These findings show that tumor size for the prognosis of patients with STS differs according to each histologic grade.

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KEY WORDS: **soft tissue sarcoma; tumor size; prognosis; histologic grade**

INTRODUCTION

In 1977, the American Joint Committee on Cancer (AJCC) proposed a staging system for soft tissue sarcoma (STS) to enable more reasonable therapeutic decisions [1]. Several factors, including histologic grade [1–3], tumor size [4–8], tumor depth [9–15], sex [13,14,16,17], and tumor-related symptoms [14,18], have been reported to be important in prognoses. Tumor size has been reported to be important by some investigators [4–8,19], but not by others [20–22]. The largest series with multivariate analysis from Sloan-Kettering [6,7], as well as the recent series by Coindre et al. [8], clearly confirm the adverse prognostic significance of size.

Recently, we developed a new and objective grading system for STS (OSAKA grade) [23]: tumors are divided

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into three grades based on the counting of argyrophilic nucleolar organizer regions (AgNOR), which reflect proliferative activity [24], cellularity, and the extent of necrosis in the tumors. There are distinct differences between the AJCC system and the OSAKA system in the determination of histologic grade, i.e., definition of degree of differentiation is essential in the AJCC system, in which poor reproducibility or interobserver disagreement occurs. Meanwhile, histologic grading in the OSAKA system is defined by more objective factors. In our previous multivariate analysis for determining important factors in the staging of STS, only the histologic grade proved to be an independent factor significant for prognosis. Clinical factors including age, tumor size, tumor depth, tumor location, tumor-related symptoms, and duration of symptoms were not significant in the staging of STS [3].

In the present study, we evaluated the significance of tumor size in combination with tumor depth in each histologic grade of STS. Two working hypotheses were set: (1) tumor size significant for prognosis might be different in each histologic grade, and (2) significance of tumor size was determined by tumor resectability, which is greatly affected by the depth of tumor, i.e., large-size but superficially located tumors could be grouped due to their relatively easier resectability than deeply located tumors.

MATERIALS AND METHODS

Patients

A total of 192 patients with localized STS in the extremities and trunk were examined. Twenty-six patients were excluded from the present study, because clinical data including tumor size and tumor depth were not available. The patients were admitted to 16 hospitals in the Osaka and Hyogo prefectures during the period 1962–1989. Clinical and histologic data in these patients have been reported previously [3]. Patient ages ranged from 15 to 84 (median 46.5) years with a peak incidence in the fifth decade of life. The male-to-female ratio was 1.19. Distribution of histologic grade, based on the criteria proposed by us [3], is shown in Table I. Tumors were located in the upper extremities in 24 cases, in the trunk in 58, and in the lower extremities in 80: 123 tumors were deeply seated, below the deep fascia, and 34 tumors were located superficial to the deep fascia. Tumor size was <5 cm in 60 cases, 5–10 cm in 58 and >10 cm in 41. Fifty-three patients had low grade STS, 51 intermediate grade, and 58 high grade. Wide local excision was performed in 73 patients (25 patients with low grade STS, 21 with intermediate grade, and 27 with high grade), and intralesional or marginal excision in 89 patients (28 with low grade STS, 30 with intermediate grade, and 31 with high grade). Fifty-one patients were treated with adjuvant chemotherapy, 14 with adjuvant radiotherapy, 13 with both adjuvant chemo- and radiotherapy. Adjuvant chemotherapy mainly consisted of Adriamycin (ADR) with or without cisplatinum (CDDP), cyclophosphamide plus vincristine (VCR) plus ADR plus DTIC (CYVADIC) or of ifosphamide (IFO) plus VCR plus ADR plus DTIC (IFOVADIC). Adjuvant radiotherapy was performed in 15 out of 93 patients by intracapsular or marginal excision and 12 out of 69 patients by wide local excision. Radiotherapy was performed preoperatively in four patients and postoperatively in 21. Radiation doses ranged from 2,800 to 5,000 cGy (mean, 4,314 cGy).

TABLE I. Distribution of Sex, Age, and Histologic Subtypes of Tumors in Each Grade

	Low grade	Intermediate grade	High grade
No. of patients	53	51	58
Sex			
male	28	25	34
female	25	26	24
Age (years) (median)	15–83 (46)	16–82 (48)	15–84 (44)
Histologic subtypes			
fibrosarcoma	2	1	2
malignant fibrous histiocytoma	14	28	18
liposarcoma	21	2	2
leiomyosarcoma	7	3	2
rhabdomyosarcoma	1	1	2
malignant vascular tumors	1	1	2
synovial sarcoma	3	4	16
malignant neurogenic tumors	1	5	8
unclassified sarcoma	1	0	2
others[a]	2	6	4

[a]Extraskeletal chondrosarcoma (low-0, intermediate-3, high-2), alveolar soft-tissue sarcoma (1,0,0), clear cell sarcoma (0,2,2) and epithelioid sarcoma (1,1,0).

Clinical Analysis

Russell et al. [1] used the tumor size dichotomized at 5 cm according to the American Joint Committee (AJCC) system. Gustafson et al. [25] found that a 10 cm dichotomization was prognostically useful. For convenience of application of the current results on future studies, we used the popular dichotomization at 5 cm and 10 cm. Two types of categorization were employed (Fig. 1), and utilities in predicting the prognosis of patients in each grade were evaluated. In the first category, tumors were dichotomized at 10 cm: Group A comprised patients with deeply seated tumors measuring >10 cm; Group B comprised patients other than those in Group A. In the second category, tumors were dichotomized at 5 cm: Group C comprised patients with deeply seated tumors >5 cm in size; Group D comprised patients other than those in Group C.

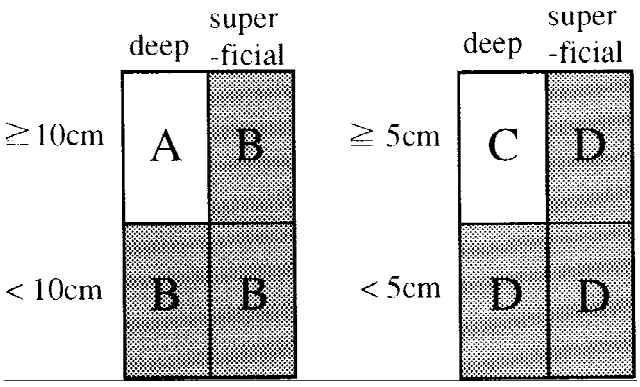

Fig. 1. Group A comprised deeply seated soft tissue sarcomas measuring >10 cm; and others as Group B. Group C comprised deeply seated tumors measuring >5 cm; and others as Group D.

Statistical Methods

The follow-up period calculated from the date of initial surgical treatment for survivors was >5 years in 51 patients and <5 years in 50, and ranged from 6 to 240 (median 60) months. In the low grade group, the follow-up period ranged from 7 to 240 (median 77) months, 6 to 231 (median 62) in the intermediate grade group, and 6 to 133 (median 36) in the high grade group, respectively. Death due to the tumor was defined as death directly attributable to the spread of the disease, not including death due to complications of treatment such as bleeding, infection, or organ failure caused by the toxicity of chemotherapeutic agents. Survival curves were calculated by the method of Kaplan and Meier [26], and the differences were evaluated by the log-rank test to analyze the significant prognostic factors [27,28]. Significance was evaluated by the Chi-square test with the criterion of $P < 0.05$.

RESULTS

Low Grade Group

Categorization of tumor size and depth was not significant for prognosis in this group.

Intermediate Grade Group

The 5-year survival rate in group B patients (78%) was higher than in group A patients (59%)($P < 0.05$) (Fig. 2), showing that dichotomization at 10 cm was useful. There were no significant differences in the distribution of age, sex, or histologic subtypes between Group A and Group B patients. The median interval between initial surgical procedures and distant metastasis in Group A and Group B was 53 months and 34 months, respectively, and frequency of occurrence of metastasis in Group A and Group B was 42% (5/12) and 28% (11/39), respectively. These differences were not significant (Table II).

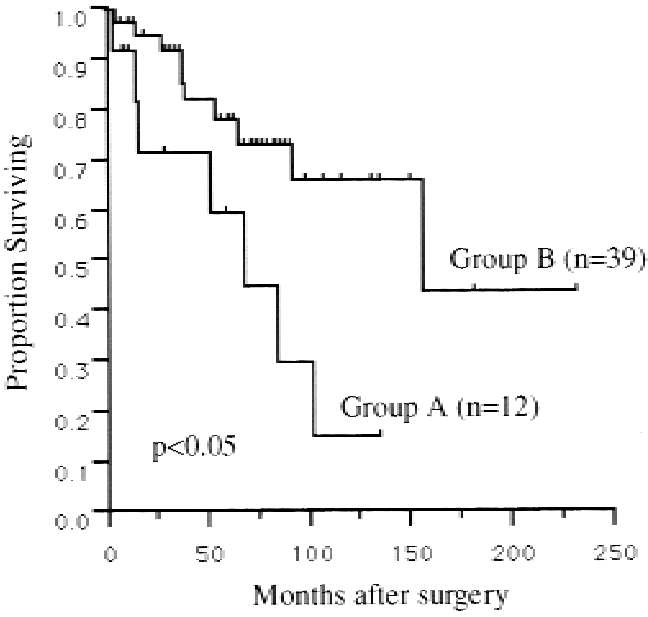

Fig. 2. Survival curves of patients with intermediate grade soft tissue sarcomas. Group A patients showed a worse prognosis than Group B. The 5-year survival rate was 59% for Group A patients, and 78% for Group B ($P < 0.05$).

TABLE II. Clinicopathologic Findings in Patients With Intermediate and High Grade Tumors

	Intermediate grade		High grade	
	Group A	Group B	Group C	Group D
Total number of patients	12	39	36	22
male	6	18	21	14
female	6	21	15	8
Metastasized cases (%)	5 (42)	11 (28)	30 (83)	10 (45)
Initial surgical procedure (metastasized cases)				
marginal excision	6 (3)	25 (9)	18 (18)	14 (6)
wide local excision	6 (2)	14 (2)	19 (12)	8 (4)
5-year survival rate (%)	59	78	32	56

High Grade Group

The 5-year survival rate in Group C patients (32%) was lower than in Group D patients (56%, $P < 0.05$) (Fig. 3), showing that dichotomization at 5 cm was useful. There were no significant differences in histologic and clinical factors between patients in Group C and D. The median interval between initial surgical procedures and distant metastasis in Group C and Group D was 14 months and 13 months, respectively. Frequency of metastasis was higher in Group C (30/36, 83%) than in Group D (10/22, 45%)($P < 0.005$)(Table II). In Group C, the frequency rate of distant metastasis was lower in patients receiving wide local excision or amputation (12/18, 67%) than in those receiving marginal or intracapsular excision (18/18, 100%)($P < 0.05$).

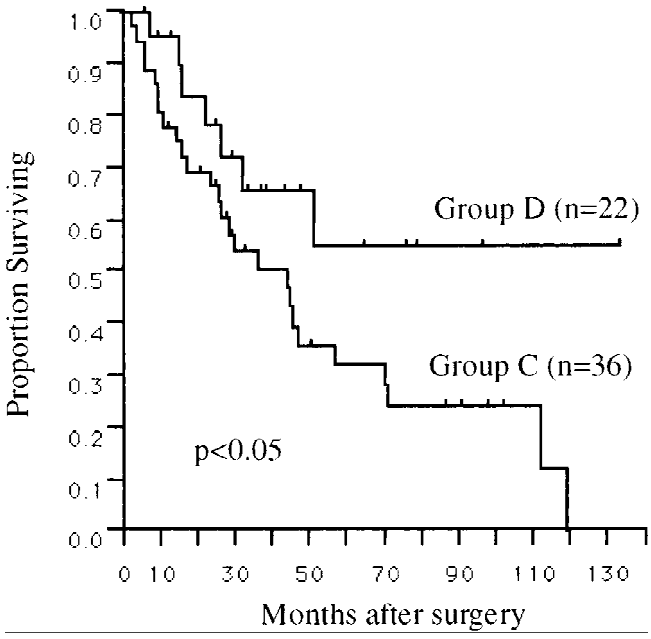

Fig. 3. Survival curves of patients with high grade soft tissue sarcomas. Group C showed a worse prognosis than Group D. The 5-year survival rate was 32% for Group C patients, and 56% for Group D patients ($P < 0.05$).

DISCUSSION

Previous studies, including our own, have shown that the histologic grade was the most important factor for the staging classification of STS [6,8,20–22,29]. In our grading system, the number of patients belonging to the low, intermediate, and high grade was similar [23]. In our previous study, only the 5 cm dichotomization of tumor size was evaluated as a prognostic factor. Therefore, dichotomization of tumors at not only 5 cm but also 10 cm was carried out in the current study, and its prognostic usefulness in our grading system was evaluated.

There have been many reports regarding the prognostic significance of tumor size in patients with STS. Tumor size has been reported to be an independent factor by some authors [4,8,25,30], whereas others disagree [2–22]. In addition, among investigators who insist that tumor size is prognostically significant, the size of dichotomization differed. Some investigators have proposed the 10 cm dichotomization to be prognostically significant [4,25,29,30]. Pisters et al. [7] and Coindre et al. [8] dichotomized tumor size at 5 cm and 10 cm; tumor size ≧5 cm had an adverse effect on overall survival, tumor size ≧10 cm was an unfavorable sign for distant metastasis [8], or tumor size >10 cm was an adverse factor for postmetastasis survival [7]. Gustafson et al. [25] made histologic grading of 354 cases with STS; I + II: 59, III: 79, IV: 200 cases (16 patients were excluded because of metastases at diagnosis of the primary tumor). Some grade II and IV cases together with all grade III cases in their grading system seemed to belong to the intermediate grade in our system, showing relatively higher frequency of intermediate grade tumors. This might be one reason why 10 cm dichotomization was useful for the prognosis of their patients as in our cases with intermediate grade STS. In contrast, in high grade tumors, 5 cm dichotomization was useful in our cases, which is identical to that reported by Gaynor et al. [6]: 239 of their 353 cases were high grade.

In the intermediate grade, Group A patients (42%) showed a higher frequency rate of metastasis than Group B patients (28%), but with a longer interval in Group A (53 months) than in Group B (34 months). In the high grade, Group C patients (83%) showed a significantly higher frequency rate of metastasis than Group D patients (45%) with almost a similar interval for development of metastasis between the two Groups: 14 months and 13 months, respectively. These findings are in agreement with Gaynor et al. [6] that the duration for occurrence of metastasis depends on the histologic grade and frequency rate and largely on the size and depth of tumors.

In conclusion, the present findings show that tumor size significant for prognosis of patients with STS is different among intermediate (10 cm) and high grade (5 cm) tumors. In each grade, large and deeply seated tumors showed a higher frequency of metastasis.

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